REMARKS

Claims 1-5, 9, 23 and 27-37 are pending in this application. Claims 35-37 have been added.

New claim 35 recites a dosage range of about 5 mg to 25 mg per day, and is supported by the specification at page 24, lines 24-26.

New claim 36 recites a dosage of about 10 mg per day and new claim 37 recites a dosage of about 5 mg per day. These claims are supported by the specification at page 24, lines 24-26.

No new matter is added by these amendments. Entry of the amendments is respectfully requested.

I. Claims Rejections under 35 U.S.C. § 103

A. Claims 1, 9, 27-30 and 33-34 are Patentable over Omoigui in view of Olmarker *et al.*

Claims 1, 9, 27-30 and 33-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Omoigui (U.S. 2004/0038874, "Omoigui") in view of Olmarker, *et al.* (WO 2002/080891, "Olmarker") (Office Action, page 5). Applicant respectfully disagrees.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. *KSR International Co. v. Teleflex Inc.*, 127 L.Ed.2d 705, 82 U.S.P.Q.2d 1385 (2007). In *KSR*, the Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. *Id.* at 1395. According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, on May 3, 2007, the Deputy Commissioner of Patents circulated a memorandum ("USPTO Memorandum," copy enclosed) to the Technology Center Directors pointing out that the TSM test was not completely abolished in *KSR*.

The *Graham* factual inquiries, which establish a guide for determining obviousness, are: (1) determine the scope and contents of the prior art; (2) ascertain

the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR*, 82 U.S.P.Q.2d at 1395 (*citing Graham*, 383 U.S. at 15-17).

The instant claims are not obvious because the references cited by the Examiner differ substantially from the subject matter of the instant claims. Furthermore, the scope and content of the references cited by the Examiner do not provide a reason that would have prompted one of ordinary skill in the art to combine the teachings of Omoigui and Olmarker to arrive at the methods of the instant claims.

1. The methods of the instant claims differ substantially from that of Omoigui in view of Olmarker.

In *KSR*, the Supreme Court noted the significance of the specific facts in question. Indeed, the District Court found that the invention at issue was simply a combination of two known elements from the prior art. *KSR*, 82 U.S.P.Q.2d at 1396. Once these specific findings were made, the Court then determined whether it was obvious to combine the teaching of the prior art to arrive at the claimed invention. *Id.* Thus, the threshold issue to be resolved is the differences between the claims at issue and the prior art.

This case is not a simple combination of two known elements. Instead, the claims at issue relate to novel methods of treating a specific disease—complex regional pain syndrome—using a specific amount (about 5 to about 50 mg per day) of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, alone or in combination with another agent or therapy. The prior art must teach or suggest each element of the claims.

The Examiner alleges that claims 1, 9, 27-30 and 33-34 are obvious because Omoigui teaches the use of TNF-α inhibitors, including thalidomide derivatives, to treat complex regional pain syndrome, and Olmarker discloses that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione may be used to treat low back pain. (Office Action, pages 5-6). Applicant respectfully disagrees. As admitted by the Examiner, Omoigui is silent as to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or its use. (Office Action, page 5). Omoigui merely discloses that thalidomide and its analogs mainly inhibit TNF- α synthesis, but the drugs also have effects on different cytokines. (Omoigui, paragraph 23). However, Omoigui does not provide a definition for or working examples to illustrate what it means by

"thalidomide analogs." Indeed, Omoigui provides no guidance to one skilled in the art to select the specific compound, much less specific amounts of the specific compound as recited in instant claim 1, to treat complex regional pain syndrome. Thus, Omoigui is missing essential elements of the claimed invention. [1]

Olmarker does not cure the deficiency of Omoigui. Olmarker merely discloses that TNF-α inhibitors may be used to treat low back pain. Olmarker does not disclose or suggest the use of the specific compound in specific amounts for treating complex regional pain syndrome as recited in instant claim 1.

The Examiner alleges that Olmarker discloses a dosage range (10-300 mg) that overlaps with the specific dosage range of the instant claims. (Office Action, page 7). Applicant respectfully points out that Olmarker teaches a dosage range of 50-1200 mg for CDC-501, which is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (page 11, line 30). Furthermore, Olmarker teaches that a dosage of 200-800 mg is "more preferred," and a dosage of 400-600 mg is "most preferred." *Id.* "[I]t is improper to combine references where the references teach away from their combination." MPEP § 2145 (citing *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983)). One skilled in the art, reading Olmarker, would select dosage ranges of 200-800 mg or 400-600 mg, which are far greater than dosages of about 5 mg to 50 mg as claimed. Thus, the dosage range disclosed by Olmarker for the specific compound of the instant claims teaches away from the dosages of the instant claims.[2]

Therefore, because substantial differences exist between the instant claims and Omoigui in view of Olmarker, the Examiner has provided no basis for the allegation that the instant claims are obvious over these references.

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[1] The focus of Omoigui is to treat pain of all kinds by mediating the inflammatory response with any of hundreds or thousands of drugs that may impact inflammation. This broad and all encompassing teaching can hardly be said to focus on thalidomide analogs. But even if it did, Omoigui provides no specific or general suggestion of any particular thalidomide analogs, not to mention the specific compound of the instant claims.

[2] Applicant points out that the dosages of new claim 35 (about 5 mg to 25 mg per day) and new claims 36 (about 10 mg per day) and 37 (about 5 mg per day) are certainly not taught or suggested by Olmarker.

2. The teachings of Omoigui and Olmarker would not prompt a person of ordinary skill to combine the elements to arrive at the processes of the instant claims.

In *KSR*, the Supreme Court emphasized that the "combination of familiar elements according to known methods is likely to be obvious when it yields no more than predictable results." *KSR*, 82 U.S.P.Q.2d at 1395. However, the Court cautioned that "[f]ollowing these principles may be more difficult in other cases...because the claimed subject matter may involve more than the simple substitution of one known element for another...." *Id.* at 1396. Further, "it can be important to *identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does." *Id.* (emphasis added); *see also* USPTO Memorandum ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

As established above, the instant case involves more than the "simple substitution" of known elements in the prior art because the references cited by the Examiner do not disclose each element of the instant claims. Further, the Examiner must provide a reason why one of ordinary skill in the art would combine the teachings of Omoigui and Olmarker and somehow arrive at the methods of the instant claims. The Examiner must articulate a reason why one of ordinary skill in the art would modify these references to arrive at the methods of the instant claims. *KSR*, *slip op.* p. 15; *see also* USPTO Memorandum. The Examiner has provided no reason that a person of ordinary skill would have combined the teachings of the references. Because the Examiner has not met this burden, the instant claims are not obvious. *Id.* Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

B. Claims 2-5 and 23 are Patentable over Omoigui in view of Olmarker and Merck.

Claims 2-5 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Omoigui in view of Olmarker, further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition ("Merck") (Office Action, page 7). The Examiner alleges that the instant claims are obvious because Omoigui teaches the use of thalidomide derivatives to treat complex regional pain syndrome, Olmarker discloses that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione may be used to treat low back pain, and Merck discloses that complex regional pain

syndrome may be treated with certain drugs, physical therapy and/or surgery. (Office Action, page 8). Applicant respectfully disagrees.

As discussed above, Omoigui in view of Olmarker does not teach or suggest each and every element of the instant claims. Neither Omoigui nor Olmarker discloses or suggests the specific compound in specific amounts as recited in instant claim 1, to treat complex regional pain syndrome. Merck does not cure this defect. Merck merely teaches that certain drugs, physical therapy and/or surgery may be used to treat complex regional pain syndrome. Merck does not disclose or suggest 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, not to mention specific dosage ranges for treating complex regional pain syndrome. Merck does not even suggest any method of combination therapy as claimed. Therefore, the instant claims are not obvious over Omoigui in view of Olmarker, further in view of Merck.

C. Claims 31-32 are Patentable over Omoigui in view of Olmarker and Remington.

Claims 31 and 32 stand rejected under 35 U.S.C. § 103(a) as unpatentable under Omoigui in view of Olmarker, further in view of Remington, *et al.* ("Remington") (Office Action, page 9). The Examiner alleges that because Remington discloses that different enantiomers of the same compound may possess different pharmacological activities, one skilled in the art would be motivated to combine this knowledge with the teachings of Omoigui and Olmarker, discussed above, to practice the methods of claims 31 and 32. *Id.* Applicant respectfully disagrees.

As discussed above, Omoigui in view of Olmarker does not teach or suggest the use of the specific compound in specific amounts as recited in instant claim 1, to treat complex regional pain syndrome. Remington does not cure this defect. Remington does not disclose or suggest anything about 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, not to mention specific dosage ranges for treating complex regional pain syndrome using this specific compound. Therefore, the instant claims are not obvious over Omoigui in view of Olmarker, further in view of Remington.

II. Obviousness-Type Double Patenting Rejection

Claims 1, 6 and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 1 or 4 of U.S. Patent No. 5,635,517 ("the '517 patent"), or claims 1, 5, 9, 22 and 23 of U.S. Patent No. 5,955,476 ("the '476 patent"), in view of Omoigui. (Office Action, pages 10-11). Applicant respectfully disagrees.

The claims of the '517 patent recite a method of reducing undesirable levels of TNF-α in a mammal using a species and a genus of compounds. The instant claims are drawn to methods for treating a specific disease—complex regional pain syndrome—using a specific amount of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

In *In re Baird*, the court held that the disclosure of a genus of compounds did not render obvious a specific compound within that genus. 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). Here, the Examiner himself admitted that the cited patents do not disclose methods of treating complex regional pain syndrome. (Office Action, page 11). Thus, because the claims of the '517 patent do not disclose or suggest a method of treating the specific disease of the instant claims, much less doing so with a specific amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, the subject matter of the present claims is not obvious and therefore it is patentably distinct from the claims of the '517 patent.

The claims of the '476 patent recite a method of reducing undesirable levels of inflammatory cytokines using a species and a genus of compounds in which the 3'-position is substituted by fluorine. The instant claims are drawn to methods for treating complex regional pain syndrome using a specific amount of a specific compound which is not substituted at the 3'-position with a fluorine atom. Therefore, the compound of the present claims is not encompassed by the compounds disclosed in the claims of the '476 patent, not to mention the use of the specific compound in a specific dose for the treatment of complex regional pain syndrome.

The Examiner points to Omoigui to cure the defects of the '517 and '476 patents. Omoigui merely discloses the use of any compound having TNF-α activity as a possible treatment for all pain. The disclosure of an earlier genus of compounds does not necessarily render obvious a subsequent claim to a species. *See In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Omoigui does not teach or suggest the use of the

specific compound of the instant claims, in a specific dose, for the treatment of complex regional pain syndrome. Like in *In re Baird*, a claim to a species—here a method of treating complex regional pain syndrome with a specific amount of a specific compound—is patentable over a genus. This is particularly true here where the teaching of Omoigui is so broad and general. Thus, the instant claims are patentably distinct from the claims of the '517 and '476 patents, and the rejection must be withdrawn.

CONCLUSION

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendments and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

No fee is believed due for this submission. However, should any fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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